



Neurobrucellosis: A Case Series

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Introduction

Brucellosis has been an important zoonotic disease globally. Since Brucella can infect and survive without inducing a massive inflammatory response, this Bacteria was labelled as “stealth pathogen.” Its protean and diverse clinical presentation can mimic other infectious and Non infectious diseases, posing challenges to physicians in reaching a diagnosis, and merited the label “disease of mistakes”. The complications of brucellosis are common and can involve a wide range of body organs and localization, neuro brucellosis being among the most serious ones. Awareness about the disease and the use of appropriate Brucella -specific tests can expedite the accurate diagnosis. Medical literature is flooded with numerous studies from different parts of the world, especially Those Endemic with brucellosis, addressing the clinical and complication aspects of this most widespread zoonotic disease. Among a considerable number of papers published on this topic there is a shortlist that we can consider as landmark in this field [1 , 2-7 , 8-11 , 12 , 13 , 14]. On a more specific aspect

dealing with neuro brucellosis, a couple of studies on this critical complication have been well noted in the literature [15 , 16]. Though the clinical and complication aspects have not changed, brucellosis remains a significant zoonotic disease that is emerging or re-emerging in many parts of the world. In addition, the inclusion of Brucella spp. in the potential biological weapon lists of most authorities has renewed interest in this these pathogens [17]. However, the improved knowledge and awareness, as well as the introduction of newer technology and tests, have helped detect and reveal more of such episodes in a short time [18 , 19].

Disease Synonyms and Brucella Species

Brucellosis has been known with many synonyms mainly pertaining to the geographic locations where the disease occurred, e.g., Malta fever, Gibraltar fever, Mediterranean fever, and Cyprus fever [20]. Brucella spp. are common zoonoses among domestic animals and wildlife and have been recovered from marine mammals. Though over 10 Brucella spp. have been recognized, only four have been well recognized to cause human

infections, and, together with their preferred/predominant host, they are *Brucella Melitensis* (mostly in goats, sheep, and camels), *B. abortus* (mostly in cattle), *B. suis* (mostly in swine), and *B. Canis* (in dogs). *Brucella* spp. recovered from marine animals were reported to cause human infections [20].

Virulence and Pathogenicity

The descriptive characteristics of *Brucella* species include small gram-negative coccobacilli, live intracellularly, and are facultative in aeration. In endemic area, the infection is mostly acquired by ingestion of fresh unpasteurized milk or its products, while in the nonendemic areas, it is mainly occupational due to accidents at clinical or research laboratories and contacts with infected laboratory animals. The incubation period may be long but the symptoms can appear in a short time (within 1–4 weeks). Once the organisms enter the body by various routes, they are encountered by the polymorphonuclear and mononuclear phagocytes. The intracellular location contributes to their virulence and pathogenesis, as they preferentially replicate within phagocytic cells. *Brucella* uses several mechanisms to avoid being killed and establish a survival niche within macrophages. To help evade the immune system and facilitate propagation, and persistence within macrophages and other cells, the pathogen forms *Brucella* -containing vacuoles (BCV) and inhibits the phagosome-lysosome. Subsequently, they are transported through regional lymph nodes into the circulatory system to seed and involve a wide range of body organs or systems, with tropism for the reticuloendothelial system, resulting in different clinical phases of disease [21]. Though receiving close attention, the exact nature of the immune response and protective antigens/factors involved in this disease are still being investigated, and the pathogenic mechanisms of reinfection remain

unknown. Recently, the production of cytokines, chemokines, and matrix metalloproteinases has been associated with induced osteoclastogenesis in *Brucella* arthritis and osteomyelitis, and the outer membrane protein 19 lipoprotein, together with tumour necrosis factor-alpha, was reported to be associated with astrocyte apoptosis in neurobrucellosis[22]. Since *Brucella* can infect and survive without inducing a massive inflammatory response, this bacteria was labelled as “stealth pathogen” [21 , 23].

Clinical manifestations of brucellosis

Brucellosis almost invariably causes fever, which may be associated with profuse sweats, especially at night. In endemic areas, brucellosis may be difficult to distinguish from the many other causes of fever. However, two features recognized in the nineteenth century distinguish brucellosis from other tropical fevers, such as typhoid and malaria: (1) Left untreated, the fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse. (2) The fever of brucellosis is associated with musculoskeletal symptoms and signs in about one-half of all patients. The clinical syndromes caused by the different species are similar, although *B. Melitensis* tends to be associated with a more acute and aggressive presentation and *B. suis* with focal abscess induction. *B. abortus* infections may be more insidious in onset and more likely to become chronic. *B. Canis* infections are generally regarded as less severe but, like other species, can cause serious disease such as endocarditis. The incubation period varies from 1 week to several months, and the onset of fever and other symptoms may be abrupt or insidious. In addition to experiencing fever and sweats, patients become increasingly apathetic and fatigued; lose appetite and weight; and have nonspecific myalgia, headache, and

chills. Overall, the presentation of brucellosis often fits one of three patterns: febrile illness that resembles typhoid but is less severe; fever and acute mono arthritis, typically of the hip or knee, in a young child; and long-lasting fever, misery, and low back or hip pain in an older man. In an endemic area (e.g., much of the Middle East), a patient with fever and difficulty walking into the clinic would be regarded as having brucellosis until it was proven otherwise. Focal features are present in the majority of patients. The most common are musculoskeletal pain and physical findings in the peripheral and axial skeleton (~40% of cases). Osteomyelitis more commonly involves the lumbar and low thoracic vertebrae than the cervical and high thoracic spine. Individual joints that are most commonly affected by septic arthritis are the knee, hip, sacroiliac, shoulder, and sternoclavicular joints. Osteomyelitis may also accompany septic arthritis. In addition to the usual causes of vertebral osteomyelitis or septic arthritis, the most important disease in the differential diagnosis is tuberculosis. Septic arthritis in brucellosis progresses slowly, starting with small pericapsular erosions. In the vertebrae, anterior erosions of the superior end plate are typically the first features to become evident, with eventual involvement and sclerosis of the whole vertebra. Anterior osteophytes eventually develop, but vertebral destruction or impingement on the spinal cord is rare and usually suggests tuberculosis. Other systems may be involved in a manner that resembles typhoid. About one-quarter of patients have a dry cough, usually with few changes visible on the chest x-ray, although pneumonia, empyema, intrathoracic adenopathy, or lung abscess can occur. Sputum or pleural effusion cultures are rarely positive in such cases, which respond well to standard brucellosis treatment. One-quarter of patients have hepatosplenomegaly, and 10%–20% have significant

lymphadenopathy; the differential diagnosis includes glandular fever-like illness such as that caused by Epstein-Barr virus, Toxoplasma, cytomegalovirus, HIV, or Mycobacterium tuberculosis. Up to 10% of men have acute Epididymo-orchitis, which must be distinguished from mumps and from surgical problems such as torsion. Prostatitis, inflammation of the seminal vesicles, salpingitis, and pyelonephritis all occur. There is an increased incidence of fetal loss among infected pregnant women, although teratogenicity has not been described and the tendency toward abortion is much less pronounced in humans than in farm animals. Neurologic involvement is common, with depression and lethargy whose severity may not be fully appreciated by either the patient or the physician until after treatment. A small proportion of patients develop lymphocytic meningoencephalitis that mimics neuro-tuberculosis, atypical leptospirosis, or Non infectious conditions and that may be complicated by intracerebral abscess, a variety of cranial nerve deficits, or ruptured mycotic aneurysms. Endocarditis occurs in ~1% of cases, most often affecting the aortic valve (natural or prosthetic). Any site in the body may be involved in metastatic abscess formation or inflammation; the female breast and the thyroid gland are affected particularly often. Nonspecific maculopapular rashes and other skin manifestations are uncommon and are rarely noticed by the patient even if they develop.

Complication

Brucellosis complications can involve different body sites with common localization. The routine hematological and biochemical profiles are usually within normal limits. Some elevation in liver function tests and erythrocyte sedimentation rate can be noted [3 , 7 , 11, 24 , 14].Complications of human brucellosis remains medically problematic and challenging [3 , 9 ,14

]. They present in diverse features and can occur at variable rates in the acute, subacute, or chronic clinical categories [26]. The variability in the reported rates among different studies could be attributed to the variable delay in the diagnosis of brucellosis [19 , 9]. The most involved sites of *Brucella* complications include the joints and bone, genitals of males and females, neurological, cardiac, pulmonary, and renal. Mortality is very low (<1 %) [4 , 5 , 9– 11]

Neuro-brucellosis

Neuro-brucellosis (detected in 3–5 % of patients with brucellosis) can affect both adults and children with diverse presentations, including fever, headache, meningeal signs, seizures, papilledema, coma, or paresis. Depression, psychosis, and mental fatigue are not uncommon complaints [15 , 16]. Manifestations of Neuro-brucellosis include meningitis, meningoencephalitis, brain or epidural abscess, cranial nerve involvement, myelitis, radiculoneuritis, ruptured mycotic aneurysms, vascular and demyelinating disorders. Cerebrospinal (CSF) analysis, of both adults and children, is nonspecific and can overlap with other central nervous system diseases, such as mycobacterial, viral, syphilitic, tuberculous, or fungal infections, or with Non infectious diseases, such as psychiatric problems, multiple sclerosis, and cancer [16]. The yield of *Brucella* culture from CSF is low (5–30 %). Therefore, the use of *Brucella* serology tests, especially indirect Coombs' or enzyme-linked immunosorbent assay, on CSF specimens is essential to diagnose Neuro-brucellosis [16]. With appropriate treatment, the prognosis is usually good for acute presentations and varies in the setting of chronic disease.

Case 1

Brucella presenting as acute psychosis and 8th cranial nerve palsy

32-year-old male sought medical attention with a four-day history of aberrant behaviour, irrelevant speech, and wandering tendencies. Accompanying symptoms included restlessness, impulsivity, episodic crying, and decreased sleep, with no reported psychiatric history, familial psychiatric disorders, or drug intake. Notably, the patient reported a seven-month history of decreased hearing, a concern that had not been previously addressed medically.

Upon examination, the patient was afebrile, consciousness, and oriented to time, but not place or person. A Glasgow Coma Scale score of 15/15 was noted, along with slurred and incoherent speech. Positive men in geal signs and acute psychosis features, including delusions, hallucinations, suspiciousness, and agitation, was observed. General physical examination, hemogram, kidney and liver function tests yielded unremarkable results. Contrast magnetic resonance imaging revealed bilateral temporal lobe hyper intensities with a ring-enhancing lesion in the right temporal subdural space, suggestive of encephalitis. While tubercular and viral meningoencephalitis was initially considered, the MRI findings leaned more towards tubercular meningoencephalitis.

Subsequent cerebrospinal fluid (CSF) analysis unveiled reactive CSF with lymphocytic pleocytosis (210 cells, 80% lymphocytes), elevated protein (78 mg/dl), and decreased glucose (26 mg/dl). Despite negative results in Gram staining, fungal stain, acid-fast bacilli, and routine CSF cultures, adenine deaminase were elevated (13.50 IU/L). Surprisingly, tuberculosis PCR yielded negative results. Further investigation into the patient's decreased hearing revealed a history of regular consumption of poorly cooked meat, particularly in the form of barbecues. This, coupled with evidence of moderate to severe sensor neural hearing loss as evidenced by pure

tone audiogram (Figure 3), raised suspicion of Neuro-brucellosis. Brucella antibody testing confirmed strong positivity for Brucella, with IgG and IgM levels in serum (EIA) measuring 18.51 and 15.79, respectively .CSF PCR for brucella was positive . Figure 3: Pure tone audiogram demonstrating moderate to severe SNHL. Treatment commenced with injection ceftriaxone, oral doxycycline, and rifampicin. Psychiatric consultation initiated Olanzapine (10 mg once daily), resulting in the gradual resolution of psychotic symptoms within two weeks although patients hearing issues persisted. Olanzapine was subsequently tapered off, and the patient demonstrated sustained improvement. This case underscores the intricate interplay between Neuro-brucellosis and psychiatric manifestations, emphasizing the necessity of a comprehensive diagnostic and therapeutic approach in such complex presentation.

Figure 1:



Figure 2:

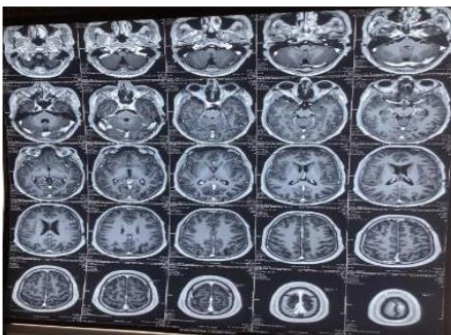
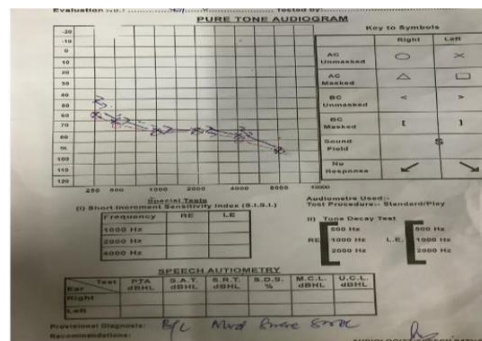


Figure 3:



Case Report 2

Brucella Myelitis

A 26 year male, presented to emergency room of this hospital with chief complaints of back ache for last two days. Back Pain was sudden in onset, mild to moderate in severity rating 3 - 5 score (out of 10 where 0 means no pain and 10 means severe pain) and burning in character, pain was radiating towards umbilicus. It was circumferential involving whole lower abdomen. Nex day in the morning when he got up from the bed and entered wash room there he felt difficulty in gripping slippers but he was able to get up from commode without difficulty. After getting out of washroom he offered prayers in the lobby As the day progressed he had slippage of slippers multiple times but he was every time conscious about it. He also noticed that while climbing upstairs his foot used to strike against step and he felt difficulty going upstairs and down stairs. There is no history of difficulty in buttoning/un buttoning, dressing, locking/unlocking, holding cup of tea, making morsel of food, getting things from overhead shelves. Weakness progressed to the extent that he was not able to get up from the sitting position and he needed support of family members to accompany him to the washroom. This weakness was associated with strong need to urinate and difficulty starting the stream of urine or keeping it flowing, increased frequency of micturition, so much that he went almost 6 to 7 times to washroom but passed only

small amount each time. On third day patient was not able to perceive sensations below the umbilicus of his clothes. Patient also complained of tightness around umbilicus. Examination revealed power 3/5 proximally and 2/5 distally in lower limbs with impaired sensations and extensor planter response on both sides.

MRI showed long segment central hyperintensity seen in the spinal cord, extending from C6 to conus medullaris.

cerebrospinal fluid (CSF) analysis unveiled reactive CSF with lymphocytic pleocytosis (210 cells, 80% lymphocytes), elevated protein (178 mg/dl), and decreased glucose (21mg/dl). Despite negative results in Gram staining, fungal stain, acid-fast bacilli, and routine CSF cultures, adenine deaminase were elevated (13.50 IU/L). tuberculosis PCR yielded negative results brucella PCR positive which suggested brucella myelitis.

Patient was treated with intravenous methylprednisolone one daily for 5 days on arrival while patient was being evaluated further. After receiving 3 doses of methylprednisolone, patient started with improvement in power by one grade. Later when diagnosis brucella myelitis was made, patient was started on iv ceftriaxone, oral rifampicin and oral doxycycline.

2 months later patient recovered completely without any weakness or any other neurodeficit

Figure 1:

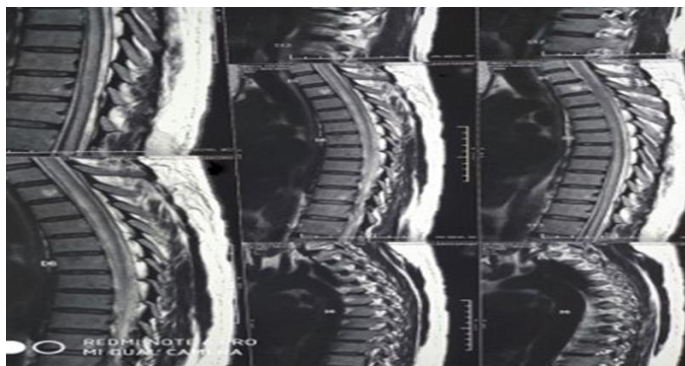


Figure 2:

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Mr. Muem Ahmed Paswal		Collected	: 10/01/24
Gender: Male		Received	: 10/01/24
unknown		Reported	: 11/10/24
148712104		Report Status	: Final
Test name	Results	Units	Bio-ref
Brucella-PCR/CFE (N)	PCR Positive	-	-
IMPORTANT INSTRUCTIONS			
All results released pertain to the specimen submitted. *All test results are dependent on the quality of the sample received. Laboratory investigations are only a tool to facilitate in arriving at a diagnosis and should be clinically correlated by the Referring Physician. Tests are accepted on request of Referring Physician within 7 days post receipt. Report delivery may be delayed.			

Case 3

Brucella Meningitis

27year male presented to outpatient department with complaints of headache for one month and vomiting for one week. He started with these complaints gradually with mild to moderate headache initially without troubling his daily activities or sleep. He described his headache as constant, bi-frontal, and throbbing in nature without any exacerbating or alleviating factors. He reported associated nausea with occasional vomiting, 7 kg weight loss, and associated thoracic back pain. Additionally, he denied fevers, tinnitus, loss of consciousness, weakness, vision loss or seizures.

On physical examination, the patient appeared well. Her temperature was 98.3°F (36.8°C), pulse was 90 beats per min, blood pressure was 113/65 mmHg, respirations were 16 breaths per min, and her oxygen saturation was 97% on room air. Her pupils were dilated at 4 mm bilaterally. Visual acuity was 20/20 in both of his right eyes and in right eye fundus grade II papilledema was noted. Examination of his left eye revealed no abnormality. The rest of her physical examination was unremarkable, Except evidence of neck rigidity but negative Kerning's and Brudzinski's signs. He refused a jolt accentuation test.

To further evaluate for infectious meningitis, a lumbar puncture was performed, which showed an opening

pressure of 35 cm H₂O. Cerebrospinal fluid (CSF) analysis revealed clear, colourless fluid, glucose of 7mg/dL (reference range 40–70 mg/dL), a total white blood cell count of 230/mm³ (reference range 0–10/mm³) with a differential of 38% neutrophils, 60% lymphocytes and protein level of 251 mg/dL (reference range 15.0–46.0 mg/dL). Additional CSF testing from the initial lumbar puncture was negative for the following tests: VDRL, flow cytometry for lymphoma, cryptococcal antigen, acid-fast bacteria (AFB) smear, CBNAAT, fungal stain, gram stain, aerobic culture and viral panel. CSF PCR for brucella was detected. A comprehensive metabolic panel and complete blood count with differential were normal, with the exception of an elevated aspartate transaminase of 106 IU/L (reference range 15–37 IU/L) and alanine transaminase of 152 IU/L (reference range 12–78 IU/L). An MRI brain with and without contrast revealed increased leptomeningeal enhancement involving the (fig1). Visual evoked potentials and audiometry revealed normal results.

Given these findings, the patient was admitted in the hospital for treatment and treatment for brucella meningitis was started. He was started on ceftriaxone, rifampicin, doxycycline. 2 weeks later patient followed up in our outpatient department, he had no further episodes of headache or vomiting. Neck had become free without any rigidity with no papilledema in either of eyes.

Case 4

Brucella Arachnoiditis

A 32-year-old lady presented with a 7-month history of gradually progressive, areflexic, asymmetric-onset, sensorimotor paraparesis accompanied by bowel and bladder involvement and truncal weakness. Two years back she had been diagnosed with uncomplicated brucellosis for which she was advised course of

doxycycline and rifampicin for 6 weeks but patient had prematurely stopped the treatment only after 2 weeks. On examination he had asymmetrical wasting and weakness of lower limbs, muscle strength of right lower limb proximally (grade 2/5), distally (grade 3/5), left lower limb proximally (grade 4/5) and distally (3/5). Minimal appendicular ataxia, absent tendon reflexes, and positive Babinski's sign. Hemogram showed lymphocytosis (49%), normal peripheral smear, and erythrocyte sedimentation rate of 74 mm/hour. Anti-nuclear antibody profile was normal. Thyroid, liver, renal functions, and serum electrolytes were normal. Serum vitamin B12 level was 647 pg/ml. Serum human immunodeficiency virus, hepatitis B surface antigen, hepatitis C virus antibodies were negative. MRI of the spine was done which revealed arachnoiditis1 (figures 1 and 2). Fundus examination was normal. Visual evoked potentials and audiometry revealed normal results. Peripheral nerve conduction studies (motor and sensory) from upper and lower limb nerves were normal. Cerebrospinal fluid (CSF) was slightly hazy and showed 170 cells/mm³ (lymphocytes = 95%; polymorphonuclear cells = 5%), protein of 478 mg/dL, and glucose of 8 mg/dL. ZN staining did not reveal acid fast bacilli, and CSF venereal disease research laboratory test was nonreactive. Serum and CSF were positive for anti-Brucella antibodies and brucella PCR as well. Blood and CSF cultures did not yield Brucella by conventional and MGIT automated method. MRI of the spine was done which revealed arachnoiditis1 (figure 1).

Patient was treated with intravenous ceftriaxone, oral rifampicin, and doxycycline. At follow-up after 4 months, patient had shown significant improvement. There was improvement in muscle strength in lower limbs by two grades. Follow-up contrast imaging showed

resolution of enhancement in the theca and along the spinal nerve roots.

Figure 1:



Case 5

Brucella Presenting As Multifocal Myelitis

A 34-year-old female came to our department with a 13-day history of inability to walk and pain in both legs. This has progressed to upper limbs also for the last 1 week along with bowel and bladder involvement such that she felt difficulty in micturition and defecation. Neurological examination revealed normal higher mental functions. Cranial nerve examination did not reveal any abnormality. Manual motor power examination revealed the following findings: Hip flexion/extension and knee flexion/extension were reduced to Medical Research Council (MRC) grade 2/5, and ankle dorsiflexion, plantar flexion, and foot inversion/eversion were reduced to MRC grade 1/5. Shoulder and elbow flexion/extension 3/5, wrist extension/flexion 1/5. The deep-tendon reflexes on the knee and ankle were absent and there was hyperesthesia and allodynia below the T1 level. The patient had urinary retention and anal reflex tone was diminished. She was thought to suffer from spinal shock due to an acute cord lesion at around T1, for which emergent spine magnetic resonance imaging (MRI) was performed. A T2-weighted thoracic spine MRI (Fig. 1 and 2) revealed hyperintense lesions in C3, T1, T4, T5, T7, T11, T12, L1 with post-contrast leptomeningeal enhancement at conus. Laboratory studies including complete blood count, and renal and liver function tests

were normal. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (a white blood cells of 130/mm³) most of them were lymphocytes (85 %) with elevated protein (138 mg/dl), low sugars (16mg/dl). Viral panel /tuberculosis work up was negative. Serum anti-aquaporin-4 (anti-AQP-4) /MOG antibody test was negative. CSF oligoclonal band analysed with concurrent serum sample and the results were negative. CSF brucella PCR was positive. Visual evoked potential test showed no conduction abnormalities. In addition, brain MRI showed

neither a pathological lesion nor an abnormally enhancing pattern. In total, other relapsing demyelinating disorders, such as NMO or multiple sclerosis were excluded. To exclude other autoimmune diseases, we evaluated autoimmune antibodies in serum. ANA, Rheumatoid factor, c-antineutrophil cytoplasmic antibodies (ANCA), p-ANCA, anti-ds DNA, the patient was finally diagnosed as having multifocal myelitis due to brucellosis. She was treated with intravenous methylprednisolone (1 g/day for 5 days). A comprehensive rehabilitation program was also prescribed. During the course of treatment the patient exhibited marked improvement of weakness by the 5th day of admission, and on the 7th day began to walk using walking aid. Her urinary retention also improved gradually. She had recovered fully from the motor weakness and urinary symptoms 12 weeks after symptom onset. In the next 6 months, she showed no suspicious symptoms of relapse.

Figure 1:

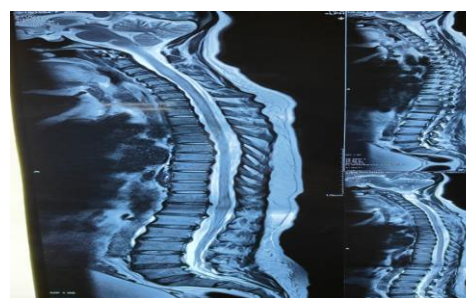
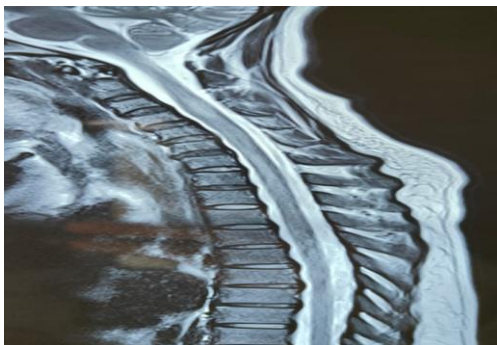


Figure 2:



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